WHOLE CELL ASSAYS AND METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 16/027,073, filed Jul. 3, 2018, which is a continuation of U.S. application Ser. No. 15/192,280, filed Jun. 24, 2016, which is a continuation of U.S. application Ser. No. 14/590,731, filed Jan. 6, 2015, which is a continuation of U.S. application Ser. No. 13/494,618, filed Jun. 12, 2012. The contents of the aforementioned applications are hereby incorporated herein by reference.

BACKGROUND

[0002] Treatment of diseased individuals has made significant progress since the discovery that chemicals and exogenous proteins can be effective human therapeutic agents against specific cellular targets. However, there is still significant room for improvement in the treatment of many common diseases such as cancer. One of the main drivers of the Human Genome Project was to discover the genetic causes of diseases, in order to advance the development and prescription of therapeutic intervention. If reports are to be believed, all human genes have been identified through the Human Genome Project. Many of these genes have been statistically linked to disease in human populations. Yet knowledge of the genetic links of a disease or detection of genetic biomarkers does not always effectively predict disease course or therapeutic outcome. So too have the genetic links and even the quantification of protein expression levels from those genes been very limited in determining appropriate therapeutic courses.

[0003] Petabyte amounts of genetic information have been collected. A great deal of statistical and analytical modeling computing power has been applied to the genetic data collected to analyze many different types of diseases. At least two important facts have emerged from this process. First, a "disease" like breast cancer is heterogeneous in part because breast cancer in one individual can be completely different from the same cancer in another individual in genetic makeup, protein expression levels, and response to therapeutic intervention. Second, detection of current genetic biomarkers has poor predictive value in the majority of cases.

[0004] Contemporary targeted drugs are discovered and developed along a process with specific limited number of human cell models in mind. Many of these cell lines are engineered to provide for optimized screening environments of large libraries of potential drugs to select those with desired activity against a particular cellular target. Employment of this process can be misleading as to the efficacy of potential drugs in light of clinical information indicating that each patient's disease is different from other patients with the same disease. The drug discovery and development process to date is not very effective at identifying responsive humans prior to clinical trials and continues to suffer a high failure rate throughout the clinical development process. Many of the drugs that are approved through the regulatory clinical development process that focuses on reducing harm to patients suffer from poor efficacy rates in actual disease patient populations.

[0005] Not all disease condition presentations to the clinical physician arise from the same cause. In a simple example, inflammation of bone joints can arise from several sources, some internal, some external, some "genetically linked," and some with yet unknown causes. The medical sciences are fairly effective in triaging patients for infectious diseases when the external pathogen can be identified properly. Physicians have fewer tools at hand for predicting which of the therapies that are currently available will lead to reduction of inflammation from internal causes. Physicians lack the knowledge of how a specific patient's cells are functioning, or more appropriately malfunctioning, and how they will respond to one of the many therapeutics that are available for treating the disease that presents clinically as "inflammation." They may know that an aberrant gene is present but do not know how that affects the disease course in a specific patient. They may know specifically how a drug is supposed to act but not why a particular patient may be unresponsive or resistant to that drug activity.

[0006] Patients need better identification of their particular disease cause and better informed decision-making for an effective therapeutic course. Human genome sequencing and other genetic quantification tools have informed doctors that each patient's disease is somewhat unique to that patient. This information has spawned a whole business around personalized medicine, where each patient could potentially receive a customized therapeutic regimen customized for their disease. Drugs are being developed for specific gene-related disease indications. This ideal approach has yet to be validated due primarily to significant shortcomings of the current prognostic toolset. The genes may be present but their function in the context of a particular individual is not correlated.

[0007] One response to the realization that each patient is different and that many times therapies fail to effect a positive response, has been the development of companion diagnostics. This type of diagnostic test is designed using contemporary biomarker detection tools to try to identify those patients that are more likely to respond to a particular drug. The test involves looking for increased gene number, gene mutation, or altered expression level of a particular gene. Success rates for most of these tests at predicting significant therapeutic response are often much less than 50%.

[0008] Thus there remains a need to provide better prognostic indicators for the effectiveness of therapeutics for an individual.

SUMMARY OF THE INVENTION

[0009] Some drugs are being targeted for specific gene-related disease indications. This approach has not yet been broadly utilized due primarily to significant shortcomings of the current prognostic toolset. The kits and methods as described herein provide for a method of selecting a therapeutic agent that shows efficacy against an individual's disease. In embodiments, the therapeutic agent is contacted to label free live whole cells from diseased tissue in a CReMS and a change or lack thereof in a physiologic parameter of the cells is detected in the presence of the therapeutic agent. A therapeutic agent is selected to treat the subject that results in a change in a physiological parameter of the disease cell as compared to a baseline measurement.

[0010] One aspect of the disclosure includes methods of selecting one or more therapeutic agents either at the initial diagnosis or throughout treatment. In embodiments, a method for selecting one or more therapeutic agents that are